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Applicant: Van Beusechem

Examiner: Scott Long

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For: VIRUSES WITH ENHANCED LYTIC POTENCY

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RESPONSE TO OFFICE ACTION

Sir:

In response to an office action mailed July 6, 2010, Applicants respectfully submit the following remarks. The response is being filed within the fourth month from the mailing date of the office action. Therefore, a petition for a one-month extension of time is being filed herewith. Reconsideration is respectfully requested.

A listing of the claims begins on page 2 of this paper.

Remarks begin on page 8 of this paper

The following is a listing of the pending claims:

1-9. Cancelled

10. (Withdrawn) The recombinant virus according to claim 1, wherein the restoring factor is chosen from the group consisting of p53, p63, p73, BAX, BAK, BOK/Mtd, BCL-Xs, Noxa/APR, PIDD, p53AIP1, PUMA, KILLER/DR5, Apaf-1, PIG, BID, tBID, BAD, HRK, Bik/Nbk, BLK, mda-7, p14ARF or functional variants, analogues or derivatives thereof.

11-14. Cancelled

15. (Withdrawn) Use of the recombinant virus according to claim 1 in a medicament.

16. (Withdrawn) Use according to claim 15 for the manufacture of a medicament for suppressing uncontrolled cell growth.

17. (Withdrawn) A method for lysing target cells hampered in the p53 dependent apoptosis pathway, comprising the steps of:

-infecting the said target cells with the replication competent recombinant virus according to claim 1, and

-replicating said virus within said target cells, further comprising the step of providing, in the virus genome, the coding sequence of at least one restoring factor functional in restoring the p53 dependent apoptosis pathway, said coding sequence being capable to be expressed in the target cells upon infection thereof by said virus.

18. Cancelled

19. (Withdrawn) The method according to claim 17, further comprising the step of subjecting said target cells to at least one of irradiation and a toxic chemical compound.

20. (Withdrawn) The method according to claim 17, wherein said target cells are present in an animal body.

21. (Withdrawn) A method for treatment of a subject body suffering from a condition involving body cells hampered in a p53 dependent apoptosis pathway, comprising the step of administering to said subject body an effective amount of the replication competent recombinant adenovirus according to claim 1.

22. (Withdrawn) The method according to claim 21, wherein the condition is associated with uncontrolled cell growth.

23. (Withdrawn) The method according to claim 22, wherein the condition is chosen from the group consisting of cancer, arthritis, and vascular smooth muscle cell hyperplasia.

24-25. Cancelled.

26. (Previously presented) A replication competent recombinant adenovirus, being capable to replicate and having lytic capacity in target cells, wherein said target cells are hampered in a p53 dependent apoptosis pathway, wherein the adenovirus is a conditionally replicating adenovirus; wherein the adenovirus genome comprises a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway in said target cells; wherein said coding sequence is operably linked to one or more expression control sequences functional in said target cells, whereby said restoring factor induces accelerated cell lysis and/or a faster release of virus progeny when compared to the recombinant adenovirus lacking said coding sequence, and wherein the virus genome further comprises a gene selected from a gene encoding the adenovirus E1B-19kDa protein or a functional analog or derivative thereof and a gene encoding the adenovirus E1B-55kDa protein or a functional analog or derivative thereof.

27. (Previously presented) The recombinant virus according to claim 26, wherein the virus is a human adenovirus.

28. (Previously presented) The recombinant virus according to claim 26, wherein expression of at least one essential early adenovirus gene is controlled by a tumor-specific promoter.

29. (Previously presented) The recombinant virus according to claim 26, wherein the adenovirus is a heterologously trans-complemented adenovirus.

30. Cancelled

31. Cancelled

32. (Previously presented) The recombinant virus according to claim 26, wherein the virus genome comprises one or more of the genes of the adenovirus E4 region encoding E4 proteins or functional analogues or derivatives thereof.

33. (Previously presented) The recombinant virus according to claim 26, wherein the virus genome comprises a gene encoding the adenovirus E1B-55kDa protein or a functional analog or derivative thereof and a gene encoding the adenovirus E4 or F6 protein or functional analogues or derivatives thereof.

34. (Previously presented) The recombinant virus according to claim 26, wherein the adenovirus carries a mutation in a E1A region encompassing at least part of the pRb-binding CR2 domain of E1A.

35. (Previously presented) The recombinant virus according to claim 26, wherein the restoring factor is p53 protein or a functional analogue or derivative thereof.

36. (Previously presented) The recombinant virus according to claim 35, wherein the protein lacks a functional binding domain for a human Mdm2 protein.

37. (Previously presented) The recombinant virus according to claim 35, wherein the protein is a functional derivative of human p53 with mutated amino acids Leu-14 and Phe-19.

38. (Previously presented) The recombinant virus according to claim 26, wherein the target cell is a human cell chosen from the group consisting of cancer cells, arthritic cells, hyperproliferative vascular smooth muscle cells and cells infected with a virus other than said recombinant virus.

39. (Previously presented) The recombinant virus according to claim 27, wherein the human adenovirus comprises serotype 5.

40. (Previously presented) The recombinant virus according to claim 34,
wherein the mutation comprises a deletion encompassing amino acids 122-129 (LTCHEAGF) of
SEQ ID NO: 5.

41. Cancelled.

REMARKS

In an office action mailed July 6, 2010, claims 26-29 and 32-40 have been rejected. In response, Applicants provide the herein remarks. Claims 26-29 and 32-40 are pending examination. Reconsideration is respectfully requested.

Applicants note that the Disposition of Claims found in the Office Action Summary contains some discrepancies as compared to the Detailed Action. From reading the Detailed Action, claims 26-40 have been rejected under §103. Claims 30 and 31 have been previously cancelled. There is no text concerning an objection of claims 35-37 and 41 as noted in the Office Action Summary.

Rejections Under §103

Claims 26-30, 32-35 and 38-40 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Curiel et al. (U.S. 6,824,771) in view of Xu et al. (Human Gene Therapy, 1997; 8:177-185). Applicants respectfully disagree with the rejection.

According to the Examiner, Curiel et al. teach a conditionally replicative recombinant adenovirus which has a functional E1B-19k and is E1B-55k-deleted or is E1A-deleted/modified and comprises a therapeutic gene operatively linked to a promoter.

The Examiner recognizes that Curiel et al. does not teach that p53 is one of the therapeutic proteins. Rather, Curiel et al. uses thymidine kinase as an exemplary therapeutic gene.

Xu et al. is cited by the Examiner to make up for the deficiencies with Curiel et al. The Examiner contends that it would have been obvious to substitute the particular anti-cancer protein, p53 from Xu et al., in the adenovirus of Curiel et al. For the following reasons, Applicants disagree with the Examiner's line of reasoning.

Curiel et al. concerns adenoviruses having a modified fiber protein. As noted in the office action, Curiel et al. does not teach adenoviruses expressing p53. It appears that Xu et al. is relied on for allegedly teaching that p53 is a therapeutic protein used to treat cancer.

The rationale used to support the combination of Curiel et al and Xu et al. is that known prior art elements are combined to yield predictable results, and that the artisan is alleged to have expected success because the molecular biology to carry out the invention was known. Applicants respectfully submit that the result of the claimed combination would not have been predicted by a skilled person, nor would a skilled person have had a reasonable expectation of success.

In the response filed June 7, 2010, Applicants provided a detailed explanation of the biology concerning replication defective p53 containing adenoviruses and oncolytic viruses.

Briefly, conditionally replicating viruses, or oncolytic viruses, are tailored to replicate specifically in tumor cells and not in normal cells.

A replication competent adenovirus needs to modify the pRb pathway in a cell in order to activate adenovirus E2 gene expression and host cell S-phase. The activation of S-phase allows replication of the adenovirus. It is thus clear that replication competent adenoviruses need to activate S-phase in a normal cell in order to replicate.

By doing so, however, the adenoviruses activate p53, which in turn inhibits adenovirus replication. Replication competent adenoviruses overcome this p53 mediated block by targeting p53 for destruction (through the action of E1B 55k and E4 orf6).

Therefore, replication competent adenoviruses need to block p53 function in order to replicate efficiently. The expression of p53 would be expected to negatively effect virus replication. In tumor cells, for example, p53 itself is often mutated or the pathway connecting pRb function to p53 function is defective. As p53 is not functional in these cells, adenoviruses do not need to shut down p53 function because it is not there from the beginning. Thus in normal cells having a functional p53 pathway, adenoviruses that are unable to block p53 function are replication competent.

By contrast, replication defective adenoviruses expressing p53 use a different mechanism to target tumor cells. In normal cells, these viruses have no effect, while when present in a tumor cell, cell cycle arrest or apoptosis is triggered.

At the time of the instant invention, it would not have been obvious to combine the teachings of Curiel et al. and Xu et al. The replicating adenoviruses of Curiel et al. do not kill cells in a p53 dependent fashion, but by other means such as autophagy and/or necrosis-like cell death. In fact, p53 is effectively inhibited and degraded by adenovirus-encoded proteins (E1B 55k, E1B19k and E4orf6).

A skilled person would expect that p53 expressed in a replication competent virus would be inhibited by said adenovirus-encoded proteins. Moreover, even if one could succeed in overcoming p53 inhibition by the adenovirus-encoded proteins, then p53 expression is expected to inhibit virus replication and thereby negate the entire concept of a conditionally replicating competent adenovirus.

Furthermore, the Examiner has previously acknowledged on page 7 of an office action mailed July 31, 2006 that “the state of the art indicates that p53 dependent apoptosis is presented through the action of E1B proteins.” Therefore, Applicants submit that it would not have been predictable or obvious to use a combination of the claimed elements.

Accordingly, at the time of invention, there was no reasonable expectation of success of conditionally replicating adenoviruses carrying tumor-suppressor genes or anti-oncogenes. The effect of the combination as established in the present invention could not be predicted and was not obvious. Indeed, the art taught away from the present invention as the combination was thought to be ineffective.

In light of the above remarks, reconsideration and withdrawal of the rejection based on Curiel et al. in view of Xu et al. is respectfully requested.

Claims 36-37 have been rejected under §103 as allegedly being unpatentable over Curiel in view of Xu as applied to claims 26 ad 35 above, and further in view of Lin et al. (Cancer Res. Oct 15, 2000. 60: 5895-5901). Applicants respectfully disagree.

Lin et al. is relied on for allegedly teaching a mutant form of human p53. As explained above, a skilled person would not have had a reasonable expectation of success in combining conditionally replicating adenoviruses with p53. Nothing in the disclosure of Lin et al. remedies this deficiency.

Therefore, in light of the above remarks, reconsideration and withdrawal of the rejection based on Curiel et al. in view of Xu et al. and further in view of Lin et al. is respectfully requested.

It is now believed that the application is in condition for allowance. If the Examiner believes a telephone discussion would be beneficial to resolve any outstanding issue, he is invited to contact the undersigned without hesitation.

Respectfully submitted,

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